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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,300	03/04/2002	Patricia Rockwell	11245/46211	1694

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,300	ROCKWELL ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,11-14,16-18,28,62 and 67-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,11-14,16-18,28,62 and 67-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 7-8, 10, 15, 19-27, 29-61 and 63-66 are cancelled.

Claims 1, 6, 11-14, 17-18, 62 and 67 have been amended.

Claims 68-69 have been added.

2. Claims 1-6, 9, 11-14, 16-18, 28, 62 and 67-69 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 9/29/05 has been considered by the Examiner. A signed copy of the IDS accompanies this Office Action.

Rejections Withdrawn

6. The rejection of claims 11-14 and 23-26 under 35 U.S.C 112, second paragraph, as the being indefinite in the recitation of "the antibody" is withdrawn in view of the amendments to the claims.

7. The rejection of claim 21 under 35 U.S.C 112, first paragraph, as containing new matter is withdrawn in view of the cancellation of the claim.

8. The rejection of claims 1, 2, 9, 11-14, 23-26, 28, 62 and 67 under 35 U.S.C. 102(e) as being anticipated by Zhu (US 2004/0259156 A1) is withdrawn in view of Applicant's arguments and amendments to the claims.

9. The rejection of claims 1-5, 9, 11-14, 16-17, 28, 62 and 67 under 35 U.S.C 103(a) as being unpatentable over Rockwell et al (Molecular and Cellular Differentiation. 3(4): 315-335, 1995, Ids filed 6/18/2003) in view of Ciardiello et al (Clinical Cancer Research, 6:3739-3747, September 2000) and Siemeister et al (Cancer and Metastasis Reviews 17: 241-248, 1998, cited previously) and Queen et al (U.S. Patent No. 5,530,101, filed 12/19/1990, cited previously) is withdrawn in view of the amendments to previously withdrawn claims 6 and 18, which now presents new limitations requiring oral administration of the VEGFR and EGFR antibodies, a limitation not taught by the above cited references and requiring new grounds of rejection as set forth below.

Priority

10. The Examiner acknowledges Applicant's updated priority claim amended on 2/1/2005. Thus, the instant claims are granted the priority date of USSN 09/798,689, (US Patent 6,811,779) i.e., 3/2/2001.

New Grounds of Rejections

11. Claims 1-6, 9, 11-14, 16-18, 28, 62 and 67-69 are rejected under 35 U.S.C 103(a) as being unpatentable over Rockwell et al (Molecular and Cellular Differentiation. 3(4): 315-335, 1995, Ids filed 6/18/2003) in view of Ciardiello et al (Clinical Cancer

Research, 6:3739-3747, September 2000, cited previously on PTO-892 mailed 3/30/05) and Siemeister et al (Cancer and Metastasis Reviews 17: 241-248, 1998, cited previously on PTO-892 mailed 12/22/03) and Thorpe et al (US Patent 6,342,219 B1, 4/28/1999).

The claims are drawn to a method of inhibiting tumor growth comprising intravenous or oral administering to a human a anti-VEGFR antibody and an anti-EGFR antibody wherein the antibodies are chimeric, humanized or human antibodies and the administration further comprises a chemotherapeutic agent or radiation and kits comprising such. Applicant is reminded that the intended use of a product claim (i.e., kit) carries no patentable weight (see MPEP 2111.02). Thus, the intended use of the kit for inhibiting tumor growth is given no patentable weight.

Rockwell et al teach that treatment of cancer with neutralizing monoclonal antibodies that block the activation of essential PTK receptors offers a promising strategy for suppressing tumor growth and tumor angiogenesis and Rockwell teaches that overexpression of EGFR correlates with poor prognosis for many cancers, including breast, prostate, non-small cell lung carcinoma, bladder, head and neck, and ovarian carcinomas (see page 317) and high levels of VEGF expression occurs in various human tumors including colorectal cancer-induced metastasis (see page 322). Rockwell et al teaches that monoclonal antibodies 225 and C225 (chimeric version of 225) that bind EGFR and inhibit ligand binding and the 225 antibody inhibits the growth of A431 (human epidermoid carcinoma) xenografts in nude mice when given within 5 days of tumor inoculation (see page 317). Rockwell et al also teach a VEGFR-specific

monoclonal antibody, DC101, which blocked VEGF receptor activation in the A431 tumor cell line (see page 322 and Figure 4A and 4B) and DC101 significantly inhibited the growth of new and established tumors (see page 323). Rockwell et al teach that DC101 is cross-reactive with human VEGFR receptor forms (i.e., flt-1 and KDR) and thus, has the potential to inhibit VEGF-mediated activation of receptors on endothelial cells induced to proliferate and form blood vessels during tumor angiogenesis (see page 323). Finally, Rockwell et al acknowledges "there is mounting preclinical and clinical data that combination therapies may be more efficacious than single agent use" (see page 327). Rockwell et al do not specifically teach combining an anti-VEGFR antibody and an anti-EGFR antibody for inhibiting tumor growth or humanized or chimeric VEGFR antibodies or intravenous or oral administration or a kit comprising the anti-VEGFR antibody and the anti-EGFR antibody. These deficiencies are made up for in the teachings of Ciardiello et al and Siemeister et al and Thorpe et al.

Ciardiello et al teach that treatment of colon cancer xenografts in mice with a VEGF antisense oligonucleotide or treatment with monoclonal antibody C225 (chimeric human-mouse IgG1) results in a mostly cytostatic and reversible growth-inhibitory effect, whereas when the two agents are used in combination, an almost complete suppression of tumor growth in all mice was observed (see page 3743, Table 2, Figures 5-7). Ciardiello et al teach that VEGF is a potent angiogenic factor and specific mitogen for endothelial cells, activates the angiogenic switch in vivo, and enhances vascular permeability and enhanced expression of VEGF has been observed in human cancer cell lines and in cancer patients with different malignancies including colorectal, breast,

non-small cell lung, and ovarian cancers and VEGF is directly correlated with increased neovascularization as measured by microvessel count within the tumor (see page 3740).

Siemeister et al teach that VEGFR receptors (flt-1 and KDR/flk-1) are up-regulated "when angiogenesis takes place, as in the case of tumor growth" (see page 243, right column). Siemeister et al teach that "the growth of malignant tumors is associated with tissue hypoxia and hypoxia has been described to be a major mechanism leading to the up-regulation of VEGF and its receptors in vivo" (see page 244). Siemeister et al teach that decreased VEGF expression in tumor cells has been achieved by blocking EGF-stimulated expression of VEGF in A431 tumor cells using an anti-EGFR neutralizing antibody (see page 245)

Thorpe et al teach anti-VEGFR blocking antibodies including chimeric, human and humanized antibodies that are less immunogenic and better suited for human therapy as compared to mouse antibodies (see entire document, particularly columns 61-70). Thorpe et al teach intravenous and oral antibody administration (see column 96 and bridging paragraph of columns 97-98) and the antibodies can be supplied in kits further comprising a chemotherapeutic or radiotherapeutic agent (see column 102).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for inhibiting tumor growth comprising administering antibodies that bind VEGFR and EGFR and further administer a chemotherapeutic agent or radiation for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a method for inhibiting tumor growth comprising administering antibodies that bind VEGFR and EGFR and further administer a chemotherapeutic agent or radiation for therapeutic benefit of human tumors in view of Rockwell et al and Ciardiello et al and Siemeister et al and Thorpe et al because Rockwell teaches EGFR- and VEGFR-specific antibodies (225 and DC101, respectively) that inhibited tumor cell growth and Ciardiello teach that inhibiting ligand (VEGF) binding to the VEGF receptor (VEGFR) or inhibiting ligand (EGF) binding to the EGF receptor (EGFR) results in a mostly cytostatic and reversible growth-inhibitory effect, whereas when ligand binding to both receptors (VEGFR and EGFR) is inhibited in combination, an almost complete suppression of tumor growth in all mice was observed and both Siemeister et al teach that interfering with VEGF signaling results in the disruption of the sequence of events involved in tumor progression and decreased VEGF expression in tumor cells has been achieved by blocking EGF-stimulated expression of VEGF in tumor cells using an anti-EGFR neutralizing antibody (see page 245). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the EGFR antibody 225 or C225 and the VEGFR antibody DC101 because Ciardiello et al teach that the combined inhibition of ligand binding to EGF and VEGF receptors significantly improved survival and almost completely suppressed tumor growth, whereas inhibition of ligand binding to the EGF receptor or ligand binding to the VEGF receptor results in mostly a cytostatic and reversible growth-inhibitory effect and

the anti-EGFR neutralizing antibody decreases EGF-stimulated expression of VEGF in tumor cells, which would interfere with VEGF signaling and disrupt the sequence of events involved in tumor progression according Siemeister, providing additional motivation for the combination of EGFR and VEGFR antibodies. Further, for human therapy one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to produce and administer intravenously or orally, chimeric, human and humanized versions of the Rockwell antibodies (225 and DC101) because such antibody forms are less immunogenic in human patients compared to mouse antibodies according to Thorpe and Rockwell teaches a chimeric version of monoclonal antibody 225 (C225; known commercially as Erbitux®) that binds EGFR with five- to ten-fold higher affinity than monoclonal antibody 225 (see page 317). Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further administer a chemotherapeutic agent or radiation because Rockwell teaches that a synergistic inhibitory affect on tumors growth was observed with monoclonal antibody 225 and a chemotherapeutic agent when compared with either agent alone and Siemeister teaches that combination treatment with anti-VEGFR monoclonal antibodies and doxorubicin results in a significant enhancement of the efficacy of either agent alone (see page 245, left column; see also Fig. 1C of Ciardiello et al). Thus, at the time the claimed invention was made it was known that combinations of substances in cancer treatment enhance the therapeutic efficacy compared with either agent alone. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced a

method for inhibiting tumor growth comprising administering intravenously or orally antibodies that bind VEGFR and EGFR and further administer a chemotherapeutic agent or radiation for therapeutic benefit of human tumors in view of the combined teachings of Rockwell et al and Ciardiello et al and Siemeister et al and Thorpe et al as a whole.

Although claims 62 and 67 recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Further, it is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy and was known by the skilled artisan at the time of the present invention as evidenced by the teachings Thorpe et al (see column 102).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments

The response filed 9/29/2005 argues that a *prima facie* case of obviousness has not been established since there is no motivation to combine the teachings of Rockwell with the teachings of Ciardiello to produce the claimed invention, i.e., method of inhibiting tumor growth by administering a combination of a VEGFR antibody and an EGFR antibody. The response acknowledges the synergistic effect upon the administration of an antisense VEGF oligonulceotide with an EGFR antibody, however, applicant argues that this does not render the claimed invention obvious and Applicant

notes that there must be some motivation or suggestion to even combine the teachings of Ciardiello with the teachings of Rockwell. Applicant states that Rockwell teach an EGFR antibody and a VEGFR antibody, but there is no suggestion to combine these antibodies for therapy. Applicant argues again that the beneficial effects of combination therapy as suggested by Rockwell are a combination of an antibody and a chemotherapeutic agent and there is no suggestion to combine an anti-VEGFR antibody with an anti-EGFR antibody as presently claimed.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. *In re Nomiya*, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 USPQ 545 (CCPA 1969). In this case, Rockwell teaches that blocking or inhibiting ligand binding to the EGFR with an anti-EGFR antibody (monoclonal antibody 225 and C225 (chimeric version of antibody 225,

also known as Erbitux®) inhibits tumor growth and blocking or inhibiting ligand binding to the VEGFR with monoclonal antibody DC101 also inhibits tumor growth, when considered in view of the teachings of Ciardiello indicating that when the ligands for both EGFR and VEGFR are blocked or inhibited, the combination produces a synergistic tumor growth inhibitory effect. Thus, there is a clear suggestion that there would be an advantage to combining the anti-EGFR antibody with the anti-VEGFR antibody to achieve a synergistic tumor inhibitory effect that significantly improves survival and almost complete suppression of tumor growth, whereas inhibition of ligand binding to EGFR alone or inhibition of ligand binding to VEGFR alone results in cytostatic and reversible growth-inhibitory effect according to Ciardiello. Applicant is reminded that the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983) (see MPEP 2144).

With respect to the teachings of Rockwell with which applicant argues, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to inhibit tumor growth by administering a combination of a VEGFR antibody and an EGFR antibody as discussed above and to further administer a chemotherapeutic agent or radiation because Rockwell teaches that a synergistic inhibitory affect of tumor growth was observed with monoclonal antibody 225 and a chemotherapeutic agent when compared with either agent alone and Siemeister

teaches that combination treatment with an anti-VEGFR monoclonal antibody and doxorubicin results in a significant enhancement of the efficacy of either agent alone.

Although Applicant does not concede that a *prima facie case* of obviousness has been established, Applicant submits a Declaration under 37 C.F.R. 1.132 by Dr. James R. Tonra providing evidence and arguments of unexpected results of the claimed invention. The Declaration and arguments submitted compare the administration of an EGFR antibody alone, a VEGFR antibody alone and a combination of the EGFR antibody and the VEGFR antibody. The response argues that the combination of the EGFR antibody and the VEGFR antibody act synergistically leading to a greater inhibition of tumor growth than either antibody administered alone (Figure 1 of the Declaration), and less of each antibody in the combination is needed to achieve 50% inhibition in tumor growth than would be expected from simply adding together the effects of the two separate treatments. Applicant concludes that the present claims yield unexpected results and are nonobvious in view of Rockwell, Ciardiello, Siemeister and Queen. This has been fully considered, but is not found persuasive. Applicant's claimed combination of an anti-EGFR antibody and an anti-VEGFR antibody are *prima facie* obvious to one of ordinary skill in the art because the evidence submitted does not prove any results beyond what one of ordinary skill in the art might have expected, and since the references strongly suggest that greater than strictly additive effects would result from the combination. As discussed above, Ciardiello teaches that when the ligands for both EGFR and VEGFR are blocked or inhibited, the combination produces a synergistic tumor inhibitory effect that significantly improves survival and results in

almost complete suppression of tumor growth, whereas inhibition of ligand binding to EGFR or inhibition of ligand binding to VEGFR results in a cytostatic and reversible growth-inhibitory effect, providing clear motivation and a suggestion that greater than strictly additive tumor inhibition would result from the combination of the anti-EGFR antibody (Mab 225 and C225 (chimeric version of Mab 225, also known commercially as Erbitux®) and the anti-VEGFR antibody, DC101, each of which are separately taught to inhibit tumor growth according to the teachings of Rockwell. Further, the benefit of using less of each antibody in the combination would have been readily apparent to one of ordinary skill in the relevant art in view of the evidence found in the references. Thus, the references on their face lead to a general expectation of greater than additive tumor inhibitory effects for the combination of an anti-EGFR antibody and an anti-VEGFR antibody. The demonstration that greater than an additive effect is obtained by combining an anti-EGFR antibody and an anti-VEGFR antibody is not in itself adequate evidence to outweigh the evidence of obviousness found in the references. The evidence submitted does not prove any results beyond what one of ordinary skill in the art might have expected adequate to rebut the *prima facie* case of obviousness. *Ex parte The Nutrasweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991). See MPEP 716.02(a).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

Conclusions

12. No claim is allowed.

13. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

SHEELA HUFF
PRIMARY EXAMINER